drugs of dependence (e.g., cocaine, morphine, and nicotine), caffeine has a lower relative dependence potential as well as a low risk of adverse effects in amounts currently permitted in foods and beverages.[116] Unlike nicotine, caffeine is not recognized as a dependence-producing substance by the American Psychiatric Association[117] and the World Health Organization.[118]

The laboratory differences between nicotine and caffeine are reflected in the different patterns of substance consumption. Neal Benowitz, a prominent addiction researcher, noted that, "[i]n contrast to coffee drinkers, the vast majority of cigarette smokers exhibit addictive behavior."[119] The wide acceptance of decaffeinated beverages demonstrates a much more general ability to control intake and minimize undesirable effects of caffeine. Moreover, while nicotine/tobacco addiction is estimated to be one of the leading causes of premature death in the United States,[120] caffeine at customary doses poses few risks to the individual or to society.

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[116] Heishman SJ, Henningfield JE, Stimulus functions of caffeine in humans: relation to dependence potential, *Neuroscience and Biobehavioral Reviews* 1992;16:273-287. *See* AR (Vol. 79 Ref. 230).

Benowitz NL, Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[117] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. (Washington DC: American Psychiatric Association, 1994), at 176. *See* AR (Vol. 37 Ref. 8).

[118] WHO, *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines* (Geneva: World Health Organization, 1992), at 75-76. *See* AR (Vol. 43 Ref. 175).

[119] Benowitz NL, Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437, at 430. *See* AR (Vol. 535 Ref. 96, vol. III.A).

[120] McGinnis JM, Foege WH, Actual causes of death in the United States, *Journal of the American Medical Association* 1993;270(18):2207-2212. *See* AR (Vol. 2 Ref. 15-1).

Hearing on Preventive Health: An Ounce of Prevention Saves a Pound of Cure, Before the Special Committee on Aging, U.S. Senate, 103d Cong., 1st Sess. 2 (May 6, 1993) (statement of Roger Herdman, Maria Hewitt, Mary Laschober, on smoking-related deaths and financial costs: Office of Technology Assessment estimates for 1990). *See* AR (Vol. 170 Ref. 2024).

Thus, the average tobacco consumer—but not the average coffee drinker—uses tobacco despite severe health risks, a clinical sign of addiction.[121]

In summary, widely publicized laboratory studies show that tobacco use, like heroin and cocaine use, is a behavioral-pharmacological process in which the individual's continued consumption of tobacco is controlled by a psychoactive and reinforcing drug that exerts its control through the central nervous system. Thus, nicotine is similar to other addictive drugs in every relevant aspect. For this reason, every scientific authority that has reviewed the results of the laboratory evidence has concluded that nicotine is addictive.

ii. Epidemiological Data Establish That Many Tobacco Users Are Addicted.

Numerous well-publicized studies and health surveys have documented the characteristics of nicotine dependence among tobacco users. In the United States, clinical criteria to assess addiction come from the DSM-IV published by the American Psychiatric Association.

Several large studies have confirmed that most cigarette smokers qualify for a diagnosis of nicotine dependence. As described in depth in the appendix to the Jurisdictional Analysis, and discussed further in section II.B.2.a., below, as many as 92% of smokers are addicted to cigarettes.[122] Smokers are more likely to become addicted than

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[121] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. (Washington DC: American Psychiatric Association, 1994), at 181. *See* AR (Vol. 37 Ref. 8).

[122] *See* appendix 1 to Jurisdictional Analysis, at 42-47. *See* AR (Vol. 1 Appendix 1).

In the Jurisdictional Analysis (60 FR 41576), FDA referred to rates of dependence among "frequent smokers" as being in the range of 75% to 90%. In this document, FDA does not use "frequent" but rather describes the definition of smokers used in each study. *See* section II.B.2., below.

users of other dependence-producing drugs, including cocaine, alcohol, marijuana, inhalants, and heroin.[123] Consistent with the results from these large studies, which assessed the prevalence of nicotine dependence as defined by meeting three or more of the seven criteria for addiction, are the findings of other studies that assessed the proportion of tobacco users meeting individual criteria. Of the seven criteria listed in section II.A.3.b., above, DSM-IV observes that six are readily apparent among tobacco users: desire to quit or unsuccessful efforts to cut down, use continued despite medical problems, a great deal of time spent using, use of substance in larger amounts and longer than intended, withdrawal, and tolerance.[124] These results strongly support the conclusion that addiction to nicotine is widespread among smokers.

Although there have been no population-based studies using criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) to assess rates of addiction to smokeless tobacco, substantial evidence demonstrates that a high proportion of smokeless tobacco users meet individual DSM criteria for addiction. This evidence strongly supports the conclusion that a substantial proportion of such users are addicted. In 1992, the Inspector General of the Department of Health and Human Services estimated that approximately 75% of young regular users of smokeless tobacco are addicted.[125]

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[123] Anthony JC, Warner LA, Kessler RC, Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: basic findings from the National Comorbidity Survey, *Experimental and Clinical Psychopharmacology* 1994;2:244-268. *See* AR (Vol. 37 Ref. 4).

[124] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 243. *See* AR (Vol. 37 Ref. 8).

[125] Department of Health and Human Services, Office on Smoking and Health, *Spit Tobacco and Youth* (Washington DC: GPO, 1992), at 8. *See* AR (Vol. 7 Ref. 76).

Data demonstrating that a high proportion of smokers and users of smokeless tobacco meet individual DSM criteria for addiction are now discussed.

Desire to quit or unsuccessful efforts to cut down. Each year, more than 15 million people in the United States—almost one-third of all daily smokers—try to quit smoking. Fewer than 3% of smokers achieve 1 year of abstinence.[126]

Quitting smokeless tobacco is also difficult. In one study, only 2.3% of smokeless tobacco users at a cessation clinic were able to remain abstinent for 6 months; the study concluded that using smokeless tobacco may be more addicting than cigarette smoking.[127]

The Centers for Disease Control and Prevention (CDC) found that the greater the level of use of the tobacco product, the more likely young people were to report that "it's really hard to quit." This increase in difficulty quitting as the amount of tobacco consumed increases demonstrates a dose-response relationship, one of the characteristic features of pharmacological effects. This dose-response relationship holds true for both cigarettes and smokeless tobacco used by 10- to 22-year-olds. For example, 74% of young people who used smokeless tobacco every day reported that it was very difficult to quit, compared to only 11% who used smokeless tobacco 1 to 14 days a month.[128]

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[126] Centers for Disease Control and Prevention, Smoking cessation during previous year among adults—United States, 1990 and 1991, *Morbidity and Mortality Weekly Report* 1993;42(26):504-507. *See* AR (Vol. 66 Ref. 2).

[127] Glover ED, Glover PN, Smokeless tobacco cessation and nicotine reduction therapy, in *Smokeless Tobacco or Health, an International Perspective,* Smoking and Tobacco Control, *NIDA Research Monograph* 2, NIH Publication No. 93-3461 (Rockville MD: Government Printing Office, 1993), at 291-295. *See* AR (Vol. 7 Ref. 79-1).

[128] Centers for Disease Control and Prevention, Reasons for tobacco use and symptoms of nicotine withdrawal among adolescents and young adult tobacco users—United States, 1993, *Morbidity and Mortality Weekly Report* 1994;43(41):745-750. *See* AR (Vol. 7 Ref. 86).

Additional studies on the common desire to quit and the failure of the vast majority of attempts can be found in appendix 1 to Jurisdictional Analysis.[129]

Use continued despite medical problems. As many as 90% of smokers know that tobacco products are harmful to their own health, 65% of current smokers believe that smoking "has already affected" their health, and 77% of smokers believe that they could "avoid or decrease serious health problems from smoking" if they quit.[130] Yet they keep smoking.

Consumers of smokeless tobacco also recognize the health risks of their tobacco use, but do not stop. In one study, 96% of young men who regularly used smokeless tobacco agreed that chewing tobacco and snuff can cause cancer.[131] Another study of users age 17 and over revealed that 77.4% believe that smokeless tobacco is a health hazard.[132]

People even continue tobacco use in the face of life-threatening, tobacco-related illnesses. For example, studies have shown that about half of smokers who have had

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[129] *See* appendix 1 to Jurisdictional Analysis, at 52-55. *See* AR (Vol. 1 Appendix 1).

[130] Gallup GH, *Smoking Prevalence, Beliefs, and Activities by Gender and Other Demographic Indicators* (Princeton NJ: Gallup Organization, 1993). *See* AR (Vol. 38 Ref. 43a).

[131] Department of Health and Human Services, Office on Smoking and Health, *Preventing Tobacco Use Among Young People: A Report of the Surgeon General* (Washington DC: Government Printing Office, 1994), at 101. *See* AR (Vol. 133 Ref. 1596).

[132] Novotny TE, Pierce JP, Fiore MC, *et al.*, Smokeless tobacco use in the United States: the adult use of tobacco surveys, *Monographs/National Cancer Institute* 1989;8:25-28. *See* AR (Vol. 41 Ref. 109).

surgery for lung cancer resume smoking[133] and that almost 40% of smokers who have had their larynxes removed try smoking again.[134]

Additional data on the use of tobacco products despite the health problems they have caused are presented in appendix 1 to the Jurisdictional Analysis.[135]

Great deal of time spent using. Studies have demonstrated that tobacco users consume tobacco regularly and compulsively. For example, 90% of smokers consume five or more cigarettes every day.[136] Over two-thirds of smokers who consume five cigarettes a day smoke their first cigarette within the first half-hour after awakening;[137] according to many experts, this need is a key symptom indicating a very significant level of dependence.[138]

Among users of chewing tobacco and moist snuff over 18, half use the products every day, and the proportion of daily users rises with age.[139] The Inspector General of

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[133] Davison G, Duffy M, Smoking habits of long term survivors of surgery for lung cancer, *Thorax* 1982;37:331-333. *See* AR (Vol. 6 Ref. 58).

[134] West R, Himbury S, Smoking habits after laryngectomy, *British Medical Journal* 1985;291:514-515. *See* AR (Vol. 6 Ref. 59).

[135] *See* appendix 1 to Jurisdictional Analysis, at 56-58. *See* AR (Vol. 1 Appendix 1).

[136] Benowitz NL, Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437. *See* AR (Vol. 535 Ref. 96, vol. III.A).

Henningfield JE, Cohen C, Slade JD, Is nicotine more addictive than cocaine? *British Journal of Addiction* 1991;86:565-569. *See* AR (Vol. 277 Ref. 3904).

[137] Giovino GA, Zhu BP, Tomar S, *et al.*, *Epidemiology of Tobacco Use and Symptoms of Nicotine Addiction in the United States: A Compilation of Data from Large National Surveys*, presentation of the Centers for Disease Control and Prevention to the FDA's Drug Abuse Advisory Committee (Aug. 2, 1994), slide 19 (from National Health Interview Survey 1987). *See* AR (Vol. 459 Ref. 7820).

[138] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), 245. *See* AR (Vol. 37 Ref. 8).

[139] Department of Health and Human Services, National Center for Health Statistics, *Vital and Health Statistics: Smoking and Other Tobacco Use: United States, 1987*, Series 10: Data from the National

the U.S. Department of Health and Human Services reported that "our 1986 and 1992 users typically held their dip or chaw 25 to 30 minutes, with most keeping it in over 30 minutes, and often up to one hour."[140]

Use of substance in larger amounts or longer than intended. Few beginning smokers plan to become daily smokers. Yet 90% of current smokers consume at least five cigarettes a day.[141] Smokers also smoke for longer periods than they intend. Among high school seniors from the Monitoring the Future Project (1976–86), almost half of the daily smokers reported that they would either probably or definitely not be smoking 5 years after graduation.[142] In a follow-up study conducted 5 to 6 years after graduation, more than two-thirds were smoking as frequently or more frequently than they had in high school (26% were smoking at the same level, and 40% were smoking more).[143]

Other evidence that users of cigarettes and smokeless tobacco consume more than they intend comes from surveys demonstrating that many people try to quit but fail. For

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Health Survey, No. 169, Sep. 1989, DHHS Publication No. (PHS) 89-1597 (Washington DC: Government Printing Office, 1989), at 24, 26. *See* AR (Vol. 711 Ref. 9).

[140] Department of Health and Human Services, Office on Smoking and Health, *Spit Tobacco and Youth* (Washington DC: Government Printing Office, 1992), at 7. *See* AR (Vol. 7 Ref. 76).

[141] Benowitz NL, Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437. *See* AR (Vol. 535 Ref. 96, vol. III.A).

Henningfield JE, Cohen C, Slade JD, Is nicotine more addictive than cocaine? *British Journal of Addiction* 1991;86:565-569. *See* AR (Vol. 277 Ref. 3904).

[142] Elders MJ, Perry CL, Eriksen MP, *et al.*, The report of the Surgeon General: preventing tobacco use among young people, *American Journal of Public Health* 1994;84(4):543-547, at 544. *See* AR (Vol. 38 Ref. 39).

[143] *Id.*

example, two of every five adult users of smokeless tobacco have tried to quit.[144] Additional studies are discussed in detail in appendix 1 to the Jurisdictional Analysis.[145]

Withdrawal. In addition to experimental evidence of withdrawal from nicotine described in section II.A.3.c.i., above, persuasive data from epidemiological studies also demonstrate that the vast majority of consumers who abstain from tobacco products experience withdrawal symptoms.[146]

Studies show that the symptoms of irritability, nervousness, restlessness, and increased appetite each affect over half of abstinent smokers; indeed, about half of abstinent smokers qualify for a formal diagnosis of Nicotine Withdrawal Syndrome under the *Diagnostic and Statistical Manual of Mental Disorders,* 3d ed., revised (DSM-III-R).[147] Withdrawal symptoms show a dose-response relationship; heavier smokers are more likely than light smokers to experience the symptoms of difficulty concentrating, hunger, irritability, restlessness, and sadness when they try to quit.[148] A similar dose-response relationship between the likelihood of withdrawal symptoms and the level of

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[144] Novotny TE, Pierce JP, Fiore MC, *et al.*, Smokeless tobacco use in the United States: the adult use of tobacco surveys, *Monographs/National Cancer Institute* 1989;8:25-28. *See* AR (Vol. 41 Ref. 109).

[145] *See* appendix 1 to Jurisdictional Analysis, at 48-55. *See* AR (Vol. 1 Appendix 1).

[146] *See* appendix 1 to Jurisdictional Analysis, at 58-61. *See* AR (Vol. 1 Appendix 1).

[147] Breslau N, Kilbey MM, Andreski MA, Nicotine withdrawal symptoms and psychiatric disorders: findings from an epidemiologic study of young adults, *American Journal of Psychiatry* 1992;149(4):464-469. *See* AR (Vol. 37 Ref. 18).

[148] Giovino GA, Zhu BP, Tomar S, *et al.*, *Epidemiology of Tobacco Use and Symptoms of Nicotine Addiction in the United States: A Compilation of Data from Large National Surveys*, presentation of the Centers for Disease Control and Prevention to the FDA's Drug Abuse Advisory Committee (Aug. 2, 1994), slides 27-32. *See* AR (Vol. 459 Ref. 7820).

nicotine intake was found among British schoolgirls[149] and other populations studied.[150] Most people who quit smoking relapse within 1 week,[151] when withdrawal symptoms are at or near their peak.[152]

Smokeless tobacco users typically experience withdrawal symptoms similar to those reported by smokers. In a study of young smokeless tobacco users, over 90% of daily users reported at least one symptom of nicotine withdrawal when trying to discontinue use. Restlessness and irritability were reported by half of daily users during abstinence.[153]

Tolerance. In addition to laboratory measures of tolerance to nicotine described in section II.A.3.c.i., above, epidemiological studies show that users of tobacco products require increasing amounts to maintain the same effects. The 1991 and 1992 National Household Survey on Drug Abuse found that 12% of smokers 25 years or older and 20% of smokers 12 to 24 years of age who smoke 16 to 25 cigarettes per day report feeling the need for an increased number of cigarettes over time to obtain the desired effects.[154]

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[149] McNeill AD, West RJ, Jarvis M, *et al.*, Cigarette withdrawal symptoms in adolescent smokers, *Psychopharmacology* 1986;90(4):533-536. *See* AR (Vol. 95 Ref. 683).

[150] Surgeon General's Report, 1988, at 206-207. *See* AR (Vol. 129 Ref. 1592).

[151] Hughes JR, Gulliver SB, Fenwick JW, *et al.*, Smoking cessation among self-quitters, *Health Psychology* 1992;11:331-334. *See* AR (Vol. 348 Ref. 5512).

[152] Hughes JR, Gust SW, Skoog K, *et al.*, Symptoms of tobacco withdrawal: a replication and extension, *Archives of General Psychiatry* 1991;48:52-59. *See* AR (Vol. 129 Ref. 1404).

[153] Centers for Disease Control and Prevention, Reasons for tobacco use and symptoms of nicotine withdrawal among adolescents and young adult tobacco users—United States, 1993, *Morbidity and Mortality Weekly Report* 1994;43(41):745-750. *See* AR (Vol. 7 Ref. 86).

[154] Giovino GA, Zhu BP, Tomar S, *et al.*, *Epidemiology of Tobacco Use and Symptoms of Nicotine Addiction in the United States: A Compilation of Data from Large National Surveys*, presentation of the Centers for Disease Control and Prevention to the FDA's Drug Abuse Advisory Committee (Aug. 2, 1994), slide 24. *See* AR (Vol. 459 Ref. 7820).

Among those who have tried an addictive substance at least once, people who have tried cigarettes are more likely to report the need for larger doses to get the same effect than people who have tried cocaine, marijuana, and alcohol.[155]

Most consumers of tobacco products escalate their doses over time. Whereas few cigarette smokers initially plan to be regular daily users, approximately 90% of them consume more than five cigarettes every day.[156]

Smokeless tobacco users also increase their dose of nicotine. One study showed a positive relationship among the number of years of smokeless tobacco use, the number of minutes per day of reported use, and urinary nicotine and cotinine levels.[157] (Cotinine is a major metabolite of nicotine and an indicator of nicotine absorption.) Other studies on dose escalation of tobacco products can be found in appendix 1 to the Jurisdictional Analysis.[158]

The epidemiological data demonstrate that a large proportion of tobacco users are dependent on nicotine and that overwhelming numbers of users show signs of addiction. These data complement laboratory evidence proving that nicotine is an addictive substance and have led to the nearly universal scientific recognition of nicotine as a drug whose

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[155] Henningfield JE, Clayton R, Pollin W, Involvement of tobacco in alcoholism and illicit drug use, *British Journal of Addiction* 1990;85:279-292. *See* AR (Vol. 39 Ref. 66).

[156] Benowitz NL, Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437. *See* AR (Vol. 535 Ref. 96, vol. III.A).

Henningfield JE, Cohen C, Slade JD, Is nicotine more addictive than cocaine? *British Journal of Addiction* 1991;86:565-569. *See* AR (Vol. 277 Ref. 3904).

[157] World Health Organization, *Smokeless Tobacco Control: Report of a WHO Study Group*, WHO Technical Report Series No. 773 (Geneva: WHO, 1988), 36. *See* AR (Vol. 7 Ref. 83).

[158] *See* appendix 1 to Jurisdictional Analysis, at 48-51. *See* AR (Vol. 1 Appendix 1).